World Health Organization

WHO Pharmaceuticals NEWSLETTER

2020 No. 1

WHO Vision for Medicines Safety
No country left behind: worldwide pharmacovigilance for safer medicines, safer patients

The aim of the Newsletter is to disseminate regulatory information on the safety of pharmaceutical products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Safety and Vigilance: Medicines,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pvsupport@who.int

This Newsletter is also available at:
http://www.who.int/medicines

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from the WHO global database of individual case safety reports, VigiBase.

This edition of the Newsletter includes updates on launch of an ADR Reporting App in Botswana and highlights from the Global Vaccine Safety Summit.

Contents

ISBN 978-92-4-000257-9 (electronic version)
ISBN 978-92-4-000258-6 (print version)

Suggested citation. WHO Pharmaceuticals Newsletter No.1, 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Printed in Switzerland

Table of Contents

Regulatory Matters

Safety of medicines

Signal

Feature

Alemtuzumab (genetic recombination)

Risk of cervicocephalic arterial dissection

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for alemtuzumab (MabCampath®) should be revised to include cervicocephalic arterial dissection as an adverse drug reaction.

Alemtuzumab is indicated for treatment of recurrent or refractory chronic lymphocytic leukemia.

One case of cervicocephalic arterial dissection and ischaemic stroke has been reported in a patient taking alemtuzumab in Japan during the previous three years. A causal relationship between alemtuzumab and the event could not be established.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Atezolizumab (genetic recombination)

Risk of haemophagocytic syndrome

Japan. The MHLW and the PMDA have announced that the package insert for atezolizumab (Tecentriq®) should be revised to include haemophagocytic syndrome as an adverse drug reaction.

Atezolizumab is indicated for specific types of breast cancers; unresectable, advanced or recurrent non-small cell lung cancer; and extensive-stage small cell lung cancer.

A total of eight cases of haemophagocytic syndrome have been reported in patients taking atezolizumab in Japan during the previous three years. Of the eight cases, a causal relationship between atezolizumab and the event could not be excluded for six. One fatal case has been reported, and the causal relationship could not be excluded.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 3 December 2019 *(www.pmda.go.jp/english/)*

Bilastine

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for bilastine (Bilanoa®) should be revised to include shock and anaphylaxis as adverse drug reactions.

Bilastine is indicated for allergic rhinitis, urticaria and itching accompanying cutaneous disease.

A total of six cases of shock or anaphylaxis in patients taking bilastine have been reported in Japan during the previous three years. Of the six cases, a causal relationship between the drug and the event could not be excluded for three cases. No patient mortalities have been reported. Additionally, there are a number of cases reported overseas. MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 3 December 2019 *(www.pmda.go.jp/english/)*

Estradiol (creams)

Four-week limit for use

Europe. The European Medicines Agency (EMA) has announced that the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that high-strength (0.01%) estradiol creams should only be used as a single treatment for a maximum of four weeks.

Estradiol creams are used as a topical hormone replacement therapy and is indicated to treat symptoms of vaginal atrophy in postmenopausal women.

The PRAC reviewed available data on the safety and effectiveness of high-strength estradiol-containing creams and concluded that absorption of estradiol into the bloodstream is of concern and could result in similar adverse effects to those seen with hormone replacement therapy such as endometrial hyperplasia/carcinoma, breast and ovarian cancer and thromboembolic events.

Reference:
EMA, 17 January 2020 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletter No.6, 2019: Four-week limit for use of high strength estradiol creams in EU)

Ingenol mebutate

1. Use with caution in patients with a history of skin cancer

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the Summary of Product Characteristics (SmPC) and the Package Leaflets (PL) for ingenol mebutate (Picato®) have been updated to include a warning regarding reports of basal cell carcinoma, Bowen's disease and squamous cell carcinoma. The update advises the use of ingenol mebutate

with caution in patients with a history of skin cancer.

Ingenol mebutate is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

In 2017, following results from a randomised study, the product information for ingenol mebutate was updated to reflect the potential for development of benign skin tumours (keratoacanthoma).

Additionally, an increased incidence of squamous cell carcinoma was observed in the preliminary results of an ongoing randomised study.

A meta-analysis of four randomized, double-blind, vehicle-controlled studies of the related ester, ingenol disoxate, found an increased incidence of skin cancer at 14 months in those treated with ingenol disoxate.

Patients should be advised to be vigilant for any skin lesions and to inform their doctor immediately should any occur.

Reference:
Drug Safety Newsletter, HPRA, December 2019 *(www.hpra.ie)*

2. Suspension during safety review

Europe. The EMA has recommended that patients should stop using ingenol mebutate during the period in which the PRAC is reviewing data on the risk of skin cancer.

There is concern about a possible link between the use of ingenol mebutate and the development of skin cancer. The PRAC has therefore recommended suspending the medicine's marketing authorization as a precaution and noted that alternative treatments are available.

Health-care professionals should stop prescribing ingenol mebutate, consider different treatment options, and advise patients to be vigilant for any developing skin lesions and to seek medical advice promptly should any occur.

Reference:
EMA, 17 January 2020 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletter No.6, 2019: Increased incidence of skin tumours in UK; No.5, 2019: Potential risk of skin cancer in EU; No.3, 2017)

Ipragliflozin

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for ipragliflozin containing products (Suglat® and Sujanu®) should be revised to include shock and anaphylaxis as adverse drug reactions.

Ipragliflozin is indicated to treat type 1 and 2 diabetes mellitus.

A total of two cases involving shock or anaphylaxis in patients treated with ipragliflozin have been reported in Japan during the previous three years. A causal relationship between the drug and the event could not be established in these cases.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Lamotrigine

Risk of adverse drug reactions when switching brands

New Zealand. Medsafe has announced that the product information for lamotrigine containing products (Logem® and Lamictal®) have been updated to include information on potential adverse effects that may occur when switching brands.

Lamotrigine is indicated for the treatment of epilepsy and of mood episodes with bipolar disorder.

The CARM has received cases of suicidal ideation, suicide attempt, headache, hot flushes, memory loss, rash and tiredness in patients that have switched brands of lamotrigine. Of these cases five had a fatal outcome. A causal link between switching brands of lamotrigine and these adverse reactions has not been established.

Reference:
Safety Communication, Medsafe, 20 December 2019 *(www.medsafe.govt.nz/)*

Levodopa

Risk of dopamine dysregulation syndrome

Japan. The MHLW and the PMDA have announced that the package inserts for levodopa containing products (Dopaston®, Neodopaston®, Duodopa enteral combination solution®, Stalevo® and Neodopasol Combination®) should be revised to include dopamine dysregulation syndrome as an important precaution.

Dopamine containing products are indicated to treat several conditions including Parkinson's disease, Parkinson's syndrome, akinesia, muscle rigidity, tremor, gait disturbance, language disorder, abnormal posture, pulsion and psychiatric symptom.

A total of three cases of dopamine dysregulation syndrome in patients treated with dopamine containing products have been reported in Japan during the previous three years. No patient mortalities have been reported.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Levothyroxine

Potential adverse reactions when switching brands

Ireland. The HPRA has announced that SmPC and PL for levothyroxine preparations (Eltroxin®, Levothyroxine Teva®, Oroxine® and other generic products) will be updated to include advice for patients switching brands or formulation due to the increased risk of adverse drug reactions following a potential imbalance of thyroid hormones. This follows recommendations issued by PRAC.

Levothyroxine is a thyroid hormone used to treat thyroid hormone deficiency.

Levothyroxine has a narrow therapeutic index. If a switch to a different brand or formulation is necessary, there is a need to closely monitor patients clinically and to perform thyroid function tests during the transition period.

Patients should be made aware of the symptoms that occur due to an imbalance of thyroid hormones and should be encouraged to consult their physician in the event that they experience any of these symptoms.

Reference:
Drug Safety Newsletter, HPRA, December 2019 *(www.hpra.ie)*

Mecasermin (genetic recombination)

Potential risk of benign or malignant tumours

Japan. The MHLW and the PMDA have announced that the package insert for mecasermin (genetic recombination, Somazon®) should be revised to include the potential risk of benign or malignant tumours as adverse drug reactions.

Mecasermin is indicated for improvement of hyperglycaemia, hyperinsulinemia, acanthosis nigricans, and hypertrichosis in diseases such as type A insulin-receptor abnormality and for improvement of growth disorder in diseases such as growth hormone-resistant isolated growth hormone deficiency type 1A.

No cases involving benign or malignant tumors have been reported in Japan during the previous three years. However, several published articles have suggested an association between human insulin-like growth factor-I, an ingredient of mecasermin, and occurrence of a tumour. Additionally, cases of benign or malignant tumours in patients treated with mecasermin have been reported overseas, although causality is unclear. The MHLW and PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 3 December 2019 *(www.pmda.go.jp/english/)*

Methotrexate

New measures to avoid dosing errors

Ireland. The HPRA has announced that SmPCs and PLs for methotrexate containing products (Jylamvo®, Methofill®, Methotrexate®, Metoject® and Nordimet®) will be updated to strengthen warnings regarding dosing errors and to reflect that the medicine is only to be prescribed by doctors with expertise in the use of methotrexate.

Methotrexate is indicated for the treatment of both inflammatory diseases and cancers. When used in the treatment of inflammatory diseases such as rheumatoid arthritis and psoriasis, methotrexate should be taken once a week. However, when used in the treatment of cancers, methotrexate may be taken more frequently. Errors in the prescribing or dispensing of methotrexate leads to serious consequences, including death. The risk of this medication error is well known, and several measures are already being taken, but this medication error continues to occur.

As well as the update of SmPCs and PLs, additional measures include introduction of educational materials for oral methotrexate products for both patients and health-care professionals.

Health-care professionals should provide patients with clear and complete dosing instructions on the once-weekly dosing regimen.

Reference:
Drug Safety Newsletter, HPRA, December 2019 *(www.hpra.ie)*

Modafinil

Potential risk of congenital malformations

New Zealand. Medsafe has announced that modafinil is contraindicated in patients who are pregnant or may become pregnant due to potential risk of congenital malformations when administered during pregnancy.

Modafinil is used to improve

wakefulness in people with excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnoea/hypopnoea syndrome or, shift work sleep disorder.

Modafinil may reduce the effectiveness of oral contraception due to enzyme induction. Alternative or concomitant methods of contraception are recommended during treatment with modafinil and for two months after stopping treatment.

Reference:
Prescriber Update, Medsafe, December 2019 *(www.medsafe.govt.nz/)*

(See WHO Pharmaceuticals Newsletter No.6, 2019: Potential risk of congenital malformations in Ireland)

Olmesartan medoxomil

Risk of interstitial pneumonia

Japan. The MHLW and the PMDA have announced that the package inserts for olmesartan medoxomil containing products (Olmetec® and Rezaltas®) should be revised to include interstitial pneumonia as an adverse drug reaction.

Olmesartan is indicated to treat hypertension.

A total of seven cases of interstitial pneumonia in patients treated with olmesartan medoxomil have been reported in Japan during the previous three years. No patient mortalities have been reported.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Osimertinib mesilate

Risk of congestive cardiac failure and decreased left ventricular ejection fraction

Japan. The MHLW and the PMDA have announced that the package insert for osimertinib mesilate (Tagrisso®) should be revised to include congestive cardiac failure and decreased left ventricular ejection fraction as adverse drug reactions.

Osimertinib mesilate is indicated for epidermal growth factor receptor (EGFR) gene mutation-positive inoperable or recurrent non-small cell lung cancer.

A total of 34 cases involving cardiac failure in patients treated with osimertinib mesilate have been reported in Japan during the previous three years. Of the 34 cases, a causal relationship between the drug and the event could not be excluded for seven cases. MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 3 December 2019 *(www.pmda.go.jp/english/)*

Secukinumab (genetic recombination)

Risk of erythroderma

Japan. The MHLW and the PMDA have announced that the package insert for secukinumab (genetic recombination, Cosentyx®) should be revised to include erythroderma (dermatitis exfoliative) as an adverse drug reaction.

Secukinumab is indicated to treat psoriasis vulgaris, psoriatic arthritis, pustular psoriasis and ankylosing spondylitis in patients who are not sufficiently responsive to conventional therapies.

A total of three cases of erythroderma in patients treated with secukinumab have been reported in Japan during the previous three years. For one of the cases, a causal relationship between the drug and the event could not be excluded.

MHLW/PMDA have concluded that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 21 January 2020 *(www.pmda.go.jp/english/)*

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Updated advice on monitoring ketone bodies

Ireland. The HPRA has announced the SmPC for sodium-glucose co-transporter 2 (SGLT2) inhibitors will be updated to include information on how to assess for ketoacidosis in patients who are hospitalized for major surgical procedures or acute serious medical illnesses.

SGLT2 inhibitors are indicated to treat type 2 diabetes, as monotherapy, or in combination with other diabetes medicines.

The decision was based on recommendations from the PRAC following an in-depth review. An initial review in 2016 concluded that a small risk of diabetic ketoacidosis (DKA) associated with exposure to SGLT2 inhibitors could not be excluded. In 2019, newly identified cases of DKA associated with SGLT2 inhibitors prompted further evaluation of the associated risk factors.

Additionally, here is evidence that SGLT2 inhibitors may

diminish the excretion of ketone bodies in the urine, and measurement of blood ketone levels is preferred to measurement of ketone bodies in the urine.

Reference:
Drug Safety Newsletter, HPRA, December 2019 *(www.hpra.ie)*

(See WHO Pharmaceuticals Newsletter No.1, 2018; Risk of non-traumatic amputations of the lower limbs, diabetic ketoacidosis and renal failure in Chile; No.4, 2016: Risk of serious diabetic ketoacidosis (DKA) in Singapore; No.2, 2016: Risk of diabetic ketoacidosis in EU; No.1, 2016: Risk of acid in blood and serious urinary tract infections in US)

Tocilizumab

Risk of hepatotoxicity

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for tocilizumab (Actemra®) has been updated to include more information about the risk of hepatotoxicity.

Tocilizumab is indicated for treatment of several conditions including rheumatoid arthritis, giant cell arteritis in adults and polyarticular juvenile idiopathic arthritis.

Eight cases of moderate to severe drug induced liver injury related to tocilizumab use, including acute liver failure, hepatitis and jaundice were identified. These events are considered rare and the benefit-harm profile of tocilizumab in the approved indications remains favourable.

Health-care professionals are reminded that tocilizumab is known to cause transient mild to moderate elevation of hepatic transaminases. Patients treated with tocilizumab should be closely monitored for liver adverse events and advised to seek immediate medical advice if they have signs or symptoms of hepatotoxicity such as jaundice, dark urine, itch, loss of appetite, nausea and vomiting.

Reference:
Medicines Safety Update, TGA, 10 December 2019 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletter No.6, 2019: Risk of hepatic impairment in Japan; No.5, 2019: Rare risk of hepatic injury in Ireland; No.4, 2019: Risk of hepatotoxicity in Australia and in UK)

Gabapentin, Pregabalin

Risk of serious breathing problems

USA. The US Food and Drug Administration (FDA) has requested that prescribing information for gabapentin and pregabalin products (Neurontin®, Gralise® and Horizant®) or pregabalin (Lyrica® and Lyrica CR®) are updated to add new warnings about the risk of serious breathing difficulties in patients who have respiratory risk factors. Such risk factors include the use of opioid pain medicines, conditions such as chronic obstructive pulmonary disease and being elderly.

Gabapentin and pregabalin are categorized as gabapentinoids and are indicated to treat a variety of conditions including partial seizures and nerve pain from spinal cord injury.

Patients should seek medical attention immediately if symptoms of respiratory problems such as confusion, unusual dizziness, extreme sleepiness and difficult breathing are observed.

Health-care professionals should start gabapentinoids at the lowest dose and monitor patients for symptoms of respiratory depression and sedation when co-prescribing gabapentinoids with an opioid or other central nervous system depressant such as a benzodiazepine.

Additionally, the FDA has requested drug manufacturers to conduct clinical trials to further evaluate the abuse potential, particularly in combination with opioids.

Reference:
Safety Alerts for Human Medical Products, US FDA, 19 December 2019 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletter No.6, 2017: Risk of severe respiratory depression in UK; No.5, 2016: Risk of serious breathing problems (respiratory depression) in Canada)

Ibuprofen

Risk of renal toxicity

New Zealand. Medsafe has informed health-care professionals of the risk of impaired renal function associated with the use of ibuprofen.

Ibuprofen is widely used for the temporary relief of pain or inflammation and is available over the counter and with a prescription.

The Centre for Adverse Reactions Monitoring (CARM) has received five reports of patients with acute kidney injury associated with ibuprofen in which dehydration was considered a possible contributing factor. The risk of impaired renal function is increased in patients who are dehydrated, especially children and adolescents.

When prescribing ibuprofen, health-care professionals should consider whether the patient is adequately hydrated.

Reference:
Prescriber Update, Medsafe, December 2019 *(www.medsafe.govt.nz/)*

Lorcaserin

Potential risk of cancer

USA. The FDA has issued an alert to the public informing them of results from a clinical trial that show a possible increased risk of cancer with the use of lorcaserin (Belviq® and Belviq XR®).

Lorcaserin is used in combination with a reduced-calorie diet and increased physical activity to help weight loss in adults who are obese or are overweight and have weight-related medical problems. It works by increasing feelings of fullness.

The cause of the cancer is uncertain, but the FDA is continuing to evaluate clinical trial results.

Health-care professionals should consider if the benefits of taking lorcaserin are likely to exceed the potential risks when deciding whether to prescribe or continue patients on lorcaserin.

Reference:
Safety Alerts for Human Medical Products, US FDA, 14 January 2020 *(www.fda.gov)*

Prednisolone (eye drops)

Potential risk of systemic effects

New Zealand. Medsafe has received a report of confusion and psychosis in a patient after starting treatment with prednisolone eye drops.

Prednisolone eye drops is a topical steroid indicated to treat inflammation of the eyes. It works by relieving symptoms such as swelling, redness and itching.

Although systemic effects are extremely uncommon in prednisolone eye drops, there have been rare occurrences of systemic hypercorticoidism after use of topical steroids.

Infants, pregnant and nursing women, and elderly patients are particularly at risk for systemic adverse reactions from eye drops.

Systemic absorption can be significantly reduced by: keeping the eyelid closed after instilling drops; applying gentle pressure over the tear duct following instillation; and waiting five to ten minutes between eye drops if more than one drop is required.

Reference:
Prescriber Update, Medsafe,

December 2019
(www.medsafe.govt.nz/)

Serotonin reuptake inhibitors (SRIs)

Risk of suicide related adverse events in children and adolescents

New Zealand. Medsafe has reminded health-care professionals about the risk of suicide related adverse events associated with the use of serotonin reuptake inhibitors (SRIs) in children and adolescents under the age of 18 years.

The CARM has received 27 case reports of reactions including suicidality, abdominal discomfort, confusion, dyspnoea, fever, gastroesophageal reflux, headache, malaise, panic, somnolence and tremor in patients aged under 18 years, where at least one of the suspect medicines was a serotonin reuptake inhibitor (SRIs).

SRIs are indicated to treat major depressive disorder and anxiety disorders. SRIs include selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs).

SRIs are not approved in New Zealand for use in children and adolescents for depression or anxiety. On the other hand, the Medicines Act 1981 permits an authorised prescriber to use any medicine (approved or unapproved) for the treatment in a particular patient under their care. The decision to use SRIs in children and adolescents should be made in consultation with the patient and their parents, ensuring that they are fully informed about the potential benefits and harms of taking the medicine.

The CARM has received two reports for citalopram, 19 reports for fluoxetine, three reports for sertraline and four reports for venlafaxine.

Adverse events in young patients tend to be more common and more severe, so it is important to closely monitor a child or adolescent who has been prescribed an SRI.

Reference:
Prescriber Update, Medsafe, December 2019
(www.medsafe.govt.nz/)

Tamoxifen

Drug-drug interaction with CYP2D6 inhibitors

New Zealand. Medsafe has informed health-care professionals of the potential interaction between tamoxifen and CYP2D6 inhibitors such as fluoxetine.

Tamoxifen is indicated to treat breast cancer. It is a prodrug metabolized by CYP2D6 into its active metabolite, endoxifen. Co-administration of strong CYP2D6 inhibitors reduces endoxifen levels. CYP2D6 inhibitors includes paroxetine and fluoxetine.

Health-care providers should prescribe an alternative antidepressant with little or no inhibition of CYP2D6 for patients who require antidepressant treatment while taking tamoxifen such as citalopram, escitalopram, sertraline, mirtazapine and venlafaxine.

Reference:
Prescriber Update, Medsafe, December 2019
(www.medsafe.govt.nz/)

Tramadol

Risk of opioid effects in breastfeeding babies

New Zealand. Medsafe has informed healthcare professionals of the risk of opioid adverse effects in babies that are being breastfed by mothers taking tramadol (Tramal® and Arrow-Tramadol®).

CARM has received one case of weight loss, feeding disorder and somnolence in a neonate who was breastfed by a mother taking tramadol.

Tramadol is used for the relief of moderate to severe pain.

Small amounts of tramadol are found in breast milk and the effect on infants and newborns has not been studied.

Medsafe is encouraging reporting of possible opioid effects in the baby when breastfeeding mothers receive tramadol.

Reference:
Safety Communication, Medsafe, 8 January 2020
(www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.5, 2019: Possible risk of opioid effects in breastfed babies in New Zealand; No.4, 2019: Contraindication in children: Risk of serious respiratory depression in Japan; No.1, 2018: Limited use: Only for adults of 18 years of age and older in USA)

A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 21 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC's current routine signal detection process. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 19). For information on the UMC Measures of Disproportionate reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. For more information, on the UMC Measures of Disproportionate Reporting etc., visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

Colecalciferol and insomnia

Anna Hegerius, Uppsala Monitoring Centre

Summary

Colecalciferol (vitamin D_3) is a steroid hormone mainly used for prophylaxis and treatment of vitamin D deficiency in elderly women and young children. Insomnia, defined as a disruption in the amount and quality of sleep that impairs functioning, is a major health issue affecting 50% of all people occasionally and 10-20% chronically. During a joint UMC/Lareb (the National Pharmacovigilance Centre in the Netherlands) signal detection sprint with a focus on patient reports, the MedDRA preferred term 'insomnia' was highlighted for the drug colecalciferol in VigiBase, the WHO global database of individual case safety reports. As of 11 December 2018, there were 52 reports for this drug–adverse drug reaction combination. The majority of the reports had co-reported drugs and/or reactions that may have contributed to the insomnia, but there were a few well documented cases that point to a possible causal association of colecalciferol and insomnia. In 21 cases the reaction abated when the drug was withdrawn and in seven the reaction recurred when the drug was readministered. A few reports also indicate a dose relationship since the reaction subsided when the dose was reduced. Insomnia is not labelled for colecalciferol and there are no case reports in the scientific literature to support a causal link. However, there is growing evidence that vitamin D may play a role in sleep regulation, influencing both sleep quantity and quality, although the mechanism of action by which vitamin D regulates sleep is not well understood and needs further investigation.

Introduction

Colecalciferol (vitamin D_3) is a steroid hormone used for the prophylaxis and treatment of vitamin D deficiency and as an adjunct to osteoporosis therapy. The drug is taken by both children and adults, with young children and the elderly (mainly women) being the main target groups. Vitamin D deficiency in children can have adverse health consequences, such as growth failure and rickets, and vitamin D supplementation for infants is therefore common in countries where a lack of sunlight may cause this. On the other hand, individual tolerance to vitamin D varies considerably (infants and children are generally more sensitive) and the difference between a therapeutic or a toxic concentration is relatively small.[1]

Colecalciferol is the natural precursor of the calcium-regulating hormone calcitriol, and has an important role in regulating body levels of calcium and phosphate in bone formation and bone resorption. It is produced in the skin under the influence of UV radiation, promotes calcium uptake in the small intestine and stimulates phosphate transport. It inhibits the excretion of calcium and phosphate in the kidney by promoting tubular resorption and inhibits the production of parathyroid hormone (PTH) in the parathyroids. Colecalciferol is often combined with calcium. Adverse events are generally associated with excessive intake of colecalciferol leading to hypercalcaemia.

Insomnia is defined as a disruption in the amount and quality of sleep that impairs functioning (or the

subjective experience of insufficient sleep). It is a major health problem, affecting 50% of all people occasionally and 10-20% chronically.[2] Chronic insomnia can affect the ability to undertake tasks such as going to work or school. Insomnia is more common in women than in men. Older women are at a higher risk of insomnia, potentially due to hormonal changes.[3] Primary insomnia occurs in the absence of underlying diseases or conditions and is not as common as secondary insomnia that can be related to a cause, e.g. drug use, mood disorders, restless legs syndrome, sleep apnoea, or travel across time zones.[2] There are several patient forums and personal blogs where the link between vitamin D intake and insomnia has been proposed and discussed.

Many classes of drugs are known to cause sleep disturbances, e.g. alpha- and beta blockers, corticosteroids, selective serotonin reuptake inhibitor (SSRI) antidepressants, angiotensin-converting enzyme (ACE) inhibitors, benzodiazepines, barbiturates, and opioids.

Reports in VigiBase

During a joint UMC/Lareb signal detection sprint, held in October 2016, with a focus on patient reports, the MedDRA preferred term 'insomnia' was highlighted for the drug colecalciferol in VigiBase, the WHO global database of individual case safety reports (ICSRs). The combination was deemed eligible for in-depth assessment in 2018 after having been kept under review for some time to see if more informative cases would strengthen the potential signal. As of 11 December 2018, there were 52 reports for this drug–adverse drug reaction (ADR) combination in VigiBase. Based on the overall reporting of adverse reactions for colecalciferol, and of the adverse reaction insomnia in VigiBase, the expected value for the number of reports on the combination was 38, and the association was highlighted as disproportionally reported, by IC analysis.[4]

The reports came from 18 countries across four continents; Europe (37 reports), the Americas (12), Asia (2), and Africa (1). More female than male patients were affected (75% women) and the age range was between nine days old and 79 years, with a median of 51 years. Consumers/non-healthcare professionals accounted for 73% of the reports of which 33% were serious. In 24 cases, colecalciferol was the only reported drug and in 34 cases it was the only suspected drug. The most frequently co-reported drugs were levothyroxine (5 cases), which may also cause insomnia, hydrocodone/paracetamol (4), and lisinopril (4). In a few cases the insomnia had been suspected to be caused by drug interactions.

Most co-reported reactions were anxiety (10 cases), irritability (9), abdominal pain (8), dizziness (8) and nausea (7), and there were quite a few cases where various gastrointestinal reactions, skin reactions and restlessness were co-reported. These co-reported reactions may have contributed to the insomnia. Seven cases concerned infants where colic seems to have been the primary ADR and an indirect cause of insomnia. In a handful of cases, the patient seems to have suffered from allergic reactions with many symptoms, and in two of these cases, the excipients brilliant blue (colouring agent) and mannitol were suspected. One patient had a medical history of sleep apnoea which is a risk factor for insomnia.

The vast majority of the patients were administered colecalciferol due to a vitamin D deficiency or as prophylaxis, and the dose varied to a great extent. The time to onset was reported in 26 cases, ranging from 30 seconds to five months, with a median of 2.5 days, but in 46% of these cases the reaction occurred within a day. In 21 cases the reaction abated when the drug was withdrawn, and in seven the reaction recurred when the drug was readministered.

A selection of well documented reports is presented in Table 1. Case 1 concerns an infant who was given colecalciferol drops as a vitamin supplement on two consecutive days and suffered from insomnia following each administration. The ADR resolved spontaneously after stopping the drug. No other drugs were given to the infant and no other health problem was reported.

In Case 2 an 8-year-old girl experienced sleeplessness, dizziness and excessive drinking [as in increased thirst red.] five days after taking an oral dose of colecalciferol. At the time of reporting, 11 days after the drug had been withdrawn, the patient was recovering. She had no known related medical history or concomitant medication. However, although the dose stated in the report was within the normal range, this may be a case of overdosage since the symptoms included thirst and vertigo.[1]

Case 3 describes a 79-year-old patient who, according to the primary source, "felt mind alive and infinite unable to sleep" three days after taking colecalciferol orally. Warfarin, alendronic acid and folic acid were listed as concomitant without start dates so it's reasonable to believe that the patient had been taking those for some time already. The drug was withdrawn and the insomnia disappeared but a week later the patient took another dose of the drug, the reaction recurred and the drug was withdrawn again.

Case 4 concerns a 49-year-old patient who was unable to sleep six hours after taking an oral dose of colecalciferol. The patient was recovering when the dose was reduced. The drug quetiapine, for which somnolence is labelled as an adverse effect, was listed as concomitant. However, it usually occurs during the first two weeks of treatment and then disappears, and the patient had been on quetiapine for four years. The patient had no related medical history nor past drug therapy.

Case 5 presents a 56-year-old patient with osteoporosis who started taking weekly doses of

oral colecalciferol in December and suffered from insomnia, irritability and restlessness in early January. The drug was withdrawn and the reaction abated. Six weeks later, the drug was readministered with the same outcome. The dose was then reduced, the ADR subsided and the lower dose was well tolerated.

Table 1. Characteristics of a selection of well documented case reports in VigiBase of insomnia in association with colecalciferol

Case	Reporter	Age/Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Time to onset	Action taken
1	Pharmacist	6 months/F	Colecalciferol (S)	Insomnia	0 days	Drug withdrawn, reaction abated Drug readministered, reaction recurred
2	Consumer	8/F	Colecalciferol (S)	Sleeplessness, dizziness, excessive drinking	5 days	Drug withdrawn, reactions abated
3	Physician	79/F	Colecalciferol (S) Warfarin (C) Alendronic acid (C) Folic acid (C)	Insomnia	3 days	Drug withdrawn, reaction abated Drug readministered, reaction recurred
4	Consumer	49/F	Colecalciferol (S) Quetiapine (C)	Insomnia	6 hours	Dose reduced, reaction abated
5	Pharmacist	56/F	Colecalciferol (S)	Insomnia, irritability, restlessness	A few weeks	Drug withdrawn, reactions abated Drug readministered, reactions recurred Dose reduced, Reactions abated

Literature and Labelling

Insomnia is not labelled for colecalciferol in the most recent Summary of Product Characteristics (SPC) in the United Kingdom[5] and there are no case reports in the scientific literature to support a causal link. However, there are studies which propose a connection between vitamin D and sleep regulation. Colecalciferol is a steroid hormone, and hormones are involved in the regulation of the sleep-wake cycle.[6] Furthermore, colecalciferol regulates the body levels of calcium and the symptoms of hypercalcaemia can include somnolence.[1]

Several studies have investigated the potential link between vitamin D deficiency and sleep disorders, and there is growing evidence that vitamin D may play a role in sleep regulation, influencing both sleep quantity and quality.[7,8] In one study, researchers analysed the sleep patterns and vitamin D levels among a group of older adult men and found that vitamin D deficiency was associated with less sleep overall and more disrupted sleep.[9] A study on Chinese schoolchildren concluded that low levels of vitamin D were associated with the risk of insufficient sleep.[10] This could indicate confounding by indication.

The mechanism of action by which vitamin D regulates sleep is not well understood. According to a recent review article, vitamin D binds to receptors in areas of the brainstem involved in sleep regulation. Cells in these areas play an important role in the first stages of sleep and in sleep maintenance. The enzymes controlling vitamin D activation and degradation are also expressed in the brain. Furthermore, vitamin D plays a pivotal role in the synthesis of melatonin, the pineal hormone controlling human circadian rhythms and sleep.[8] Vitamin D has also been shown to regulate the synthesis of a variety of neurotransmitters, including serotonin and dopamine, which are known to promote waking and inhibit sleep.[11,12] Dopamine can inhibit the production and release of melatonin.[13]

Discussion and Conclusion

The majority of the reports have co-reported drugs and/or reactions that may have contributed to the insomnia, and, as stated above, low levels of

vitamin D may also affect sleep and be a potential explanation for insomnia. However, case reports in VigiBase point to a possible causal association of colecalciferol and insomnia. The 52 reports came from 18 countries, and colecalciferol was the only suspected drug in 34 cases. Of the 26 reports where a time to onset was specified, 12 patients experienced the reaction insomnia within a day. In 21 cases the reaction abated when the drug was withdrawn and in seven cases the reaction recurred when the drug was readministered. A few reports also indicate a dose relationship since the reaction subsided when the dose was reduced.

Among the better documented cases shown in the table, the first one concerned an infant where no reactions other than insomnia were reported, but in all other cases concerning infants, reactions such as abdominal pain/infant colic and/or crying were co-reported. In the second selected case, the patient was a child who in addition to insomnia suffered from dizziness and increased thirst, symptoms which may indicate overdosage, particularly since the risk of toxicity is greater among children. Cases 3 and 4 have concomitant drugs, but they are unlikely to have caused the insomnia; in both cases, insomnia was the only reported reaction. For the patient in the third case, the reaction abated when the drug was withdrawn and recurred about a week later when the drug was readministered. In the fourth case, the reaction abated when the dose of colecalciferol was reduced. In the last case, colecalciferol was the only reported drug. The co-reported reactions irritability and restlessness may have contributed to the insomnia, but all reactions abated when the drug was withdrawn, recurred upon readministration, and subsided when the dose was reduced. There is thus a strong case for a causal relationship.

VigiBase case reports and studies suggest a link between vitamin D and sleep disturbances, but further investigations are needed to determine the exact mechanism of action.

References

1. Medicines Complete: Adverse effects and treatment for colecalciferol. Available from: https://www.medicinescomplete.com/#/content/martindale/7892. Accessed: 25 Mar 2019.
2. Taber's Online Medical Dictionary: Search term 'insomnia'. Available from: https://www.tabers.com/tabersonline. Accessed: 25 Mar 2019.
3. Office on women's health: Search term 'insomnia'. Available from: https://www.womenshealth.gov/a-z-topics/insomnia. Accessed: 7 May 2019.
4. Norén GN, Hopstadius J, Bate A. Shrinkage Observed-to-expected Ratios for Robust and Transparent Large-scale Pattern Discovery. Stat Methods Med Res. 2013 Feb 1;22(1):57-69.
5. Electronic Medicines Compendium: Summary of Product Characteristics for colecalciferol (Desunin®) Available from: https://www.medicines.org.uk/emc/product/7263/smpc. Accessed: 25 March 2019.
6. Terán-Pérez G, Arana-Lechuga Y, Esqueda-León E, Santana-Miranda R, Rojas-Zamorano JÁ, Velázquez Moctezuma J. Steroid Hormones and Sleep Regulation. Mini Rev Med Chem. 2012 Oct;12(11):1040-8.
7. Gao Q, Kou T, Zhuang B, Ren Y, Dong X, Wang Q. The Association between Vitamin D Deficiency and Sleep Disorders: A Systematic Review and Meta-Analysis. Nutrients. 2018 Oct 1;10(10):1395.
8. Muscogiuri G, Barrea L, Scannapieco M, Di Somma C, Scacchi M, Aimaretti G, et al. The lullaby of the sun: the role of vitamin D in sleep disturbance. Sleep Med. 2019 Feb 1;54:262-5.
9. Massa J, Stone KL, Wei EK, Harrison SL, Barrett-Connor E, Lane NE, et al. Vitamin D and Actigraphic Sleep Outcomes in Older Community-dwelling Men: the MrOS Sleep Study. *Sleep.* 2015 Feb 1;38(2):251–7.
10. Gong QH, Li SX, Li H, Chen Q, Li XY, Xu GZ. 25-Hydroxyvitamin D Status and Its Association with Sleep Duration in Chinese Schoolchildren. Nutrients. 2018 Aug 3;10(8):1013.
11. Jiang P, Zhang LH, Cai HL, Li HD, Liu YP, Tang MM, et al. Neurochemical Effects of Chronic Administration of Calcitriol in Rats. *Nutrients.* 2014; 6(12):6048-59.
12. Monti JM, Jantos H. The Roles of Dopamine and Serotonin, and of Their Receptors, in Regulating Sleep and Waking. Prog Brain Res. 2008; 172:625-46.
13. González S, Moreno-Delgado D, Moreno E, Pérez-Capote K, Franco R, Mallol J, et al. (2012) Circadian-Related Heteromerization of Adrenergic and Dopamine D4 Receptors Modulates Melatonin Synthesis and Release in the Pineal Gland. PLoS Biol. 2012;10(6).

Desogestrel and night sweats, vulvovaginal dryness and dry eye

Nadja Jastrebova and Magnus Ekelo, Uppsala Monitoring Centre

Summary

Night sweats, vulvovaginal dryness and dry eye are reported as adverse drug reactions to desogestrel, an oral contraceptive, in 53 individual case safety reports in VigiBase. There are 20 desogestrel – night sweats reports with 14 positive dechallenges, 22 desogestrel – vulvovaginal dryness reports with 12 positive dechallenges and 15 desogestrel – dry eye reports with 7 positive dechallenges. The reports, mostly provided by consumers, involve women 22 to 50 years old, where desogestrel was usually the only drug reported. Few reports provided any other possible explanation for the reactions. Several consumers described a significant negative effect on quality of life and noticeable improvement when discontinuing desogestrel. These three adverse drug reactions are already included in descriptions of some other contraceptives, but not for desogestrel, therefore it is important to communicate this signal.

Introduction

During a joint patient report signal detection screening involving Uppsala Monitoring Centre and the Netherlands Pharmacovigilance Centre Lareb, an association between desogestrel and night sweats was identified. This revived interest in two desogestrel combinations that were identified in 2016 but were kept under review at the time. These were vulvovaginal dryness and dry eye in conjunction with desogestrel.

Desogestrel is marketed in some countries as a single ingredient oral contraceptive, whereas it is only used in fixed-dose combination products together with ethinylestradiol in other parts of the world. This assessment focused on the reports where desogestrel was used as single ingredient.

Desogestrel achieves its contraceptive effect primarily by the inhibition of ovulation. Other effects include increased viscosity of the cervical mucus and decreased oestradiol levels, to one corresponding to the early follicular phase.[1] After intake, desogestrel is metabolized to its active metabolite, etonogestrel.[2] Like other progestogen-only drugs, desogestrel is best suited for use during breast feeding and for women who do not want to use oestrogens.[1]

Night sweats have been defined in several ways, all of which describes heavy sweating during the night. It is a common inconvenience during perimenopause and menopause. It can also be an adverse outcome of treatment with antidepressants and has been observed as a symptom in several diseases.[3]

Vulvovaginal dryness most commonly occurs when oestrogen levels are decreased. The cause is often perimenopause, but it can also occur during breast-feeding or as an adverse effect to treatment, such as anti-oestrogen cancer medicines, chemotherapy or oral contraceptives.[4]

Dry eye is a common condition affecting especially those older than 40 years. More women than men are affected and especially menopausal or pregnant women and those taking oral contraceptives or who are on hormone replacement therapy. Androgens and oestrogens have receptors in the lacrimal and meibomian glands and thereby influence production of tear film. Changes in sex hormone levels can affect functions of these glands and subsequently result in dry eye symptoms.[5]

These three adverse drug reactions (ADRs) affect different organs but they have a common denominator – they are frequently experienced by women during perimenopause or menopause and during other conditions when sex hormone levels are changed.

Reports in VigiBase

There were 53 reports of desogestrel and either night sweats, vulvovaginal dryness or dry eye in VigiBase at the time of the analysis, 11 November 2018. Based on the overall reporting of adverse reactions for desogestrel and of these three adverse reactions in VigiBase, the expected values for the number of reports on these combinations were 3.5 for night sweats, 0.35 for vulvovaginal dryness and 3.6 for dry eye, thus the associations were highlighted as disproportionally reported, by IC analysis (Table 1). Fifty-two reports came from nine European countries and one from Latin-America. Reporters in almost all cases (72%) were consumers. They concern women of similar age range from 22 to 50 years, median being 34, 32 and 33 for night sweats, vulvovaginal dryness and dry eye respectively (Table 1). Weight and height were provided in 22 reports, and BMI values were calculated showing normal weight for the majority of these patients, median being 21, 23 and 22 for night sweats, vulvovaginal dryness and dry eye reports respectively (normal weight BMI=18.5 to 24.9). In many cases desogestrel was the only drug reported, suggesting that affected patients were overall healthy women, not being treated for other medical conditions. Desogestrel was indicated for contraception in almost all reports where an indication was provided (Table 1). In one report with ADR night sweats, desogestrel was prescribed for endometriosis of ovary and in another with ADR vulvovaginal dryness the indication was premenstrual syndrome. The times to onset for all

reactions were typically within the first two weeks of treatment.

Table 1. Characteristics of case reports in VigiBase of reaction in association with desogestrel

	Night sweats	Vulvovaginal dryness	Dry eye
Number of reports	20	22*	15*
Number of reporting countries	6	9	5
Number of reports with only desogestrel	15	15	10
Number of expected reports	3.5	0.35	3.6
IC_{025}	1.66	3.97	1.10
Age, median (range)	34 (24 - 46)	32 (22 - 50)	33 (22 - 46)
BMI, median (range)	21 (19 - 27)	23 (18- 28)	22 (21- 29)
Indication – contraception	16	18	11
Time-to-onset, median (range)	15 (1-49 days)	7 (0 days-7 years)	2 (0 days-2 months)
Outcome, Recovered or Recovering	17	13	9
Positive dechallenge	14	12	7

**Four reports had both ADR terms vulvovaginal dryness and dry eye*

In the 15 reports where desogestrel treatment was stopped, the majority had recovered (8) or were recovering (5) from the night sweats. The time for recovery was rarely provided but a few cases mention either a rapid or gradual recovery. One patient described that when she started taking the pill in the mornings, the problem with night sweats disappeared. Desogestrel was the only drug used in 15 of the reports. Selective Serotonin Reuptake Inhibitors (SSRIs) which can cause night sweats were co-reported in three reports. The severity of the night sweats was sometimes captured in the reporter's comments. Several user stories tell of the vigorous sweating causing them to wake up during the night and depriving them of sleep. One desogestrel user reported "*I was not getting enough sleep due to waking each night dripping with sweat, overheating caused nightmares which were highly unpleasant*." Hormone levels (sometimes oestrogen) were mentioned in a few reports and "hormone level abnormal" was reported as a reaction in one, but no laboratory values were provided. "*I believe it may also be why my oestrogen levels are still low*" said one reporter (consumer).

The treatment was stopped in 13 cases, leading to improvement of vulvovaginal dryness in 11 cases, seven recovered and four recovering. In seven reports there were no stop dates for desogestrel suggesting continuation of treatment, of these five patients continued to suffer from the reaction. One of these accounts describes how the ADR had affected her life "*Patient then declares having menstrual bleeding every 15 days and vaginal dryness with increasing severity over time. (…) In the light of the consequences on the patient's personal life (discomfort and impossible sexuality), she took the decision herself to stop contraception. Effects disappeared immediately.* (translation from French).

Reporters provided information about stopping the drug in 11 cases of dry eye with the outcome recovered in four patients and recovering for three. One of the patients who stopped taking the drug and recovered, started to use Mirena (a contraceptive containing another progestogen - levonorgestrel) which led to the reappearance of the ADR. Three patients provided descriptions of the substantial negative impact this ADR had had on their lives. One of them wrote "*It's been so bad that I have been completely dependent on artificial tear fluid, and also used eye ointment at night. It has influenced my life to a large degree.... [I] would never have thought that quitting [treatment] would make the situation so much better. Noticed fairly immediately difference when I stopped, went from being completely dependent of eye drops, to not use them anymore!* (translation from Norwegian).

Literature and Labelling

Night sweats, vulvovaginal dryness and dry eye are not mentioned among possible adverse reactions to desogestrel in the UK Summary of Product Characteristics (SmPC).[1] Nor does the patient information leaflet mention these three reactions.[6] The SmPC does cover one uncommon adverse reaction within the MedDRA system organ class Eye disorders: contact lens intolerance. Vaginal infection

is listed as an uncommon adverse reaction for the vaginal tract.[1,6]

On the other hand, ADRs set out in this analysis are listed among ADRs for some combined contraceptives, which contain ethinylestradiol and a progestogen. These are products containing ethinylestradiol and norgestimate, which have night sweats, vulvovaginal dryness and dry eye in the label.[7] Products containing ethinylestradiol and drospirenone, have vaginal dryness and dry eye labelled.[8] Nuvaring contains ethinylestradiol and etonogestrel, the active metabolite of desogestrel, and has vulvovaginal dryness labelled.[9] The National Health Service in the UK lists contraceptive pills as one of the causes of vaginal dryness.[10] Contraceptive pills are also mentioned among the factors that can contribute to dry eye by the National Eye Institute of the USA.[11]

Discussion and Conclusion

Desogestrel is known to decrease oestrogen level and it might be this effect that plays a role in the development of the menopausal symptoms in these cases. They could also potentially be explained as naturally occurring perimenopause, a state when sex hormonal levels start to change, decreasing oestradiol levels being one them. Most women in this case series were of premenopausal age, ranging between 22-50 years with a median for all three reactions of 33 years. The average age at which menopause occurs is 51 years and perimenopause usually start after mid-40s, but some women already experience it in their mid-30s.[12] However, in most cases the onset of symptoms came soon after beginning of desogestrel treatment and the majority of desogestrel users saw the symptoms disappear after dechallenge, which argues against perimenopause.

Another potential risk factor leading to low oestrogen levels and associated symptoms is low weight, but available BMI values show that only one patient's weight was below the normal range (BMI <18.5). Few other medicines were taken concomitantly and therefore co-medication could not explain these reactions either. Another possible cause of one of the reactions, vulvovaginal dryness, is breast-feeding which is mentioned in two reports in the vulvovaginal dryness case series.

The three reactions discussed here have already been listed for some other contraceptives. Night sweats and vulvovaginal dryness have also been reported in VigiBase more often than expected for other progestogens (levonorgestrel, medroxyprogesterone and norethisterone), suggesting potential class effects. Tamoxifen, an anti-oestrogen used in breast cancer treatment, also causes menopausal symptoms, night sweats and vaginal dryness being two of them.[13]

The SmPC of desogestrel lists ADRs contact lens intolerance and vaginal infection. A common reason for not being able to use contact lenses is having dry eyes. Likewise, one of risk factors for vaginal infection is vaginal dryness. Therefore, although vulvovaginal dryness and dry eye are not labelled, they might be the underlying causes or parts of these symptoms, where a connection may be obvious for a health care professional, but not for a consumer. This may be the reason why vulvovaginal dryness and dry eye are mostly reported by consumers.

In conclusion, in looking at research literature, SmPCs and health online resources, vulvovaginal dryness and dry eye are already associated with use of contraceptive drugs. These case series present a short time to onset of symptoms, many positive dechallenges, not many confounders, and there is a possible mechanism behind the reactions. In addition, patients in the case series tell of vigorous sweating, vaginal dryness affecting sexual activity and being completely dependent on artificial tear fluid. Considering the consequences for the patient these reactions may cause, it is important to communicate this signal.

References

1. Electronic Medicines Compendium: Summary of Product Characteristics for Desogestrel 75 microgram Film-coated Tablets (https://www.medicines.org.uk/emc/product/6830). Accessed November 2018.
2. Drugbank: Desogestrel. https://www.drugbank.ca/drugs/DB00304. Accessed: March 2019
3. Mold JW, Holtzclaw BJ, McCarthy L. Night sweats: a systematic review of the literature. J Am Board Fam Med. 2012 Nov 1;25(6):878-93.
4. Margesson LJ. Vulvovaginal Dryness and Itching. STL 2001 Sep;6(10) (https://www.skintherapyletter.com/pruritus/vulvovaginal-dryness-itching/)
5. Peck T, Olsakovsky L, Aggarwal S. Dry Eye Syndrome in Menopause and Perimenopausal Age Group. J Midlife Health. 2017 Apr-Jun;8(2):51-4.
6. Electronic Medicines Compendium: Patient Leaflet for Desogestrel 75 microgram Film-coated Tablets (https://www.medicines.org.uk/emc/product/6830/pil). Accessed November 2018.
7. Electronic Medicines Compendium: Summary of Product Characteristics for Cilique 250/ 35 microgram tablets (https://www.medicines.org.uk/emc/product/2011) Accessed: March 2019
8. Health Products Regulatory Authority: Summary of Product Characteristics for Yaz https://www.hpra.ie/homepage/medicines/medicines-information/find-a-

medicine/results/item?pano=PA1410/056/001&t=YAZ# Accessed: March 2019

9. Electronic Medicines Compendium: Summary of Product Characteristics for Nuvaring (https://www.medicines.org.uk/emc/product/6449) Accessed: March 2019
10. National Health Service: Vaginal dryness https://www.nhs.uk/conditions/vaginal-dryness/. Accessed: March 2019
11. National Eye Institute: Dry Eye https://nei.nih.gov/health/dryeye/dryeye Accessed: March 2019
12. National Health Service: Menopause https://www.nhs.uk/conditions/menopause/ Accessed: September 2019
13. Moon Z, Hunter MS, Moss-Morris R, Hughes LD. Factors related to the experience of menopausal symptoms in women prescribed tamoxifen. J Psychosom Obstet Gynaecol. 2017 Sep;38(3):226-35

CAVEAT DOCUMENT

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs).

Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

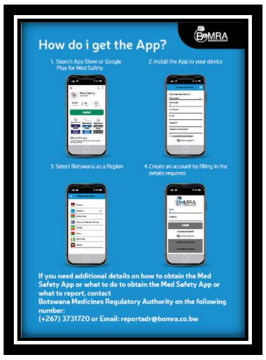
Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.
UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

Uppsala Monitoring Centre (UMC)
Box 1051, SE-751 40 Uppsala, Sweden
Tel: +46-18-65 60 60, E-mail: info@who-umc.org
www.who-umc.org

Adverse Drug Reaction (ADR) Med Safety App and E-Reporting Launch in Botswana

Dr Thabang Phetlhe, Pharmacovigilance Officer, Botswana Medicines Regulatory Authority (BoMRA),
Dr Parthasarthi Gurumurthy, Director, Post Marketing Surveillance and Control of Clinical Trials, BoMRA

The Med Safety App[1] and E-Reporting were launched during an event at the Gaborone International Convention Centre in Botswana on 14th November 2019. The event was graced by the Honourable Minister of Health and Wellness, Dr Lemogang Kwape, Botswana Medicines Regulatory Authority (BoMRA) CEO Dr Stephen Ghanie, WHO-HQ Representative Ms Ayako Fukushima and WHO Local office representative Ms Kefentse Moakofi. A total of 140 delegates attended the event, amongst them 125 were health-care professionals.



Dr Stephen Ghanie welcomed the delegates. He stated that BoMRA started operations in 2018, its objective is to be fully operational in 2020 and to reach maturity level 3 through the WHO global benchmarking by 2023.[2]

Dr Parthasarathi Gurumurthy, Director of Post Marketing Surveillance and Control of Clinical Trials, gave a brief background to medicines safety monitoring initiatives of BoMRA. He stressed that, for building a robust national pharmacovigilance program, active participation of all stakeholders and fostering the culture of reporting are essential.

Keynote Address was delivered by Hon Minister of Health, Dr Lemo Gang Kwape.

"Under reporting of adverse drug reactions (ADRs) is a recognised phenomenon and through the launch of E-Reporting, BoMRA is facilitating the reporting of ADRs by health-care professionals"

He concluded by stating that reduction of medication errors and harmful effects of medicines is of paramount importance to the Ministry of Health and Wellness and commended the BoMRA initiative.

[1] World Health Organization. Med Safety App: an international mobile tool for drug safety. *WHO Pharmaceuticals Newsletter* 2019,6:27. Available from https://www.who.int/medicines/publications/PharmaNewsletter6-19/en/

[2] WHO website: Regulatory system strengthening: https://www.who.int/medicines/regulation/rss/en/

Technical partners involved in the development of the app joined virtually from the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (UMC) in Uppsala, Sweden. They provided a presentation on how to use the app, a demonstration of E-Reporting, and shared valuable learnings from countries already using the tools. The Pharmacovigilance Advisory Committee chairperson, Dr Gontle Moleele gave closing remarks to conclude the event.

Four stations were set up for the demonstration of the Med Safety App and E-Reporting tools for participants. Attendees had the opportunity to practice reporting using the platforms and ask questions. Feedback was positive and participants looked forward to using the app particularly as it is thought to help reduce the time spent on paper-based reporting.

Further awareness activities and training took place after the launch. One hundred and ninety-six health-care professionals across the country were trained on pharmacovigilance and reporting platforms. As of 3rd February 2020, BoMRA received a total of 12 ADR reports, five reports from physicians and seven reports from pharmacists that were reported using the Med Safety app.

Global Vaccine Safety Summit: Looking to the future of vaccine safety

The Global Vaccine Safety Summit took place 2-3 December 2019 at WHO Headquarters in Geneva, Switzerland. The event combined two main streams of WHO work on vaccine safety: 1/ capacity building with the Global Vaccine Safety Initiative (GVSI); and 2/ vaccine safety science with the Global Advisory Committee on Vaccine Safety (GACVS).

The GVSI is the implementation mechanism of the Global Vaccine Safety Blueprint, WHO's strategy to build capacity so that *"everyone, everywhere who receives a dose of vaccine can communicate any safety concern and that concern can be properly handled"*. Following a broad, participative development process, the Blueprint was endorsed by the WHO Strategic Advisory Group of Experts (SAGE) in 2012. It is also identified in the Global Vaccine Action Plan as the vaccine safety strategy. As WHO looks to the next decade with the General Programme of Work (GPW) 13 and an Immunization Agenda 2030, a stakeholder survey was conducted during the first semester 2019 to evaluate the impact of the Blueprint. More than 200 respondents representing the main stakeholders (vaccine safety experts, national regulatory officials, immunization program managers, global agencies, industry, nongovernmental organizations (NGOs)) contributed, recognized the value of the GVSI and proposed approaches to render it more impactful. With the help of a drafting group, Blueprint 2.0 was developed and went through a first round of public review that gathered more than 200 comments. This second draft went public on 18 November 2019 for discussion in a Hearing format during Day 1 of the Summit. During the meeting, participants expressed broad interest on the Global Vaccine Safety Blueprint 2.0 and discussed detailed comments for each of the 6 strategic areas and the accountability framework. This enhanced strategy includes a stronger focus on communicating about vaccine safety as an additional layer that ensures the safest possible administration of vaccinations in all parts of the world. It also calls for additional resources mobilized by all concerned parties to allow the implementation of this critical agenda. A revised version of the blueprint incorporating comments and suggestions from the meeting will be prepared and presented to SAGE in April 2020.

In the year that marks the 20th anniversary of the WHO's Global Advisory Committee on Vaccine Safety (GACVS), the Global Vaccine Safety Summit was also an opportunity to take stock of GACVS accomplishments and look towards priorities for the next decade. During Day 2 of the Summit, the evolution of vaccine safety science was reviewed through four panels that discussed safety concerns from the 20th century that, for the most part, have been resolved with robust scientific data. It also explored new frontiers related to newly identified untoward effects of vaccines, the need to adapt safety monitoring systems to those new characteristics, and evolving technologies to produce more effective vaccines. Proceedings from the meeting will be published as a supplement in the BMJ Global Health.


9789240002579
9 789240 002579